38. (New) The method of claim 20, wherein said cancer is prostate cancer.

39. (New) The method of claim 20, wherein said cancer is colon cancer.

40. (New) The method of claim 20, wherein said cancer is lung cancer.

41. (New) The method of claim 21, wherein said cancer is breast cancer.

42 (New) The method of claim 21, wherein said cancer is prostate cancer.

43. (New) The method of claim 21, wherein said cancer is colon cancer.

44. (New) The method of claim 21, wherein said cancer is lung cancer.

REMARKS

Introduction

Receipt is acknowledged of the office action dated May 21, 2002. In the action, the examiner rejected claims 1-10 and 16 under 35 U.S.C. § 112 for alleged indefiniteness and non-enablement. The examiner, however, asserted that the art does not recognize the replacement of amino acids in IGF-I to inhibit the growth of cancerous tumors (office action at 3), and therefore acknowledges the novelty and non-obviousness of the present invention.

New claims 18-44 have been added in the instant application. Accordingly, claims 1-44 are pending. Support for new claims 18-24 can be found on page 5, lines 23-31 of the specification. Support for new claims 25-44 can be found on page 7, lines 1-2.

In view of the foregoing amendments and the remarks set forth below, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

35 U.S.C. § 112, 1st paragraph

The examiner rejected claims 1-10 and 16 under 35 U.S.C. § 112, for alleged non-enablement. The examiner asserted, in relevant part, that the three dimensional structure, and therefore activity, cannot be predicted based on the amino acid sequence of the peptide and that the specification has not provided any guidance as to what amino acid additions or changes should be avoided or are desired (office action at 6). The examiner also indicates that "different aspects of biological activity cannot be predicted a priori but must be determined from...case to case by painstaking experimental study" (office action at 7).

Applicant respectfully disagrees and asserts that this argument relies on the fact that the protein structure of IGF-I is unknown and that no guidance on protein/structure is available in the art. This is simply not the case for null IGF. In fact, the structures of IGF-I, IGF-II and insulin have been defined. *See*, Appendix A. Thus, the structure of new analogs can be predicted, using computer modeling with higher predictability than of a generic protein upon which no structural information is available. In other words, one is not predicting *de novo*, but is reasonably predicting the structure of any individual analog based on existing structural information.

Moreover, the regions critical for receptor binding and IGFBP binding have also been defined in the art. *See*, for example, *Jansson Biochemistry* (1997) 36:4108. At the time of filing, one skilled in the art would be able to alter amino acid residues in the binding protein and/or receptor binding domain (which are distal to each other), without substantially changing the protein structure. As long as the null IGF has the desired biological activity, the precise structure is not particularly relevant. Therefore, new IGF analogs can be designed *in silico* based on existing models of IGF and the known critical regions of the molecule. Testing the new analogs can then be accomplished by using routine binding assays for the IGF receptor and binding proteins. It is important to emphasize that "the test of enablement is not whether any experimentation is necessary, but whether,...it is undue" (M.P.E.P. § 216.04, citing *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976). Certainly given the state of the art and the level of one of ordinary skill, the amount of experimentation necessary to determine if the IGF analog retains IGFBP binding and has reduced affinity for the IGF-I receptor is not undue.

Furthermore, the specification of the instant invention provides guidance on what IGF analog activity is suitable for use in the methods of the present invention. The specification clearly teaches that null IGF is a genus of IGF analogs that have a (1) reduced affinity to the IGF receptor and (2) maintained ability to complex IGF binding proteins. So long as the null IGF shares these properties, it is suitable for use in the methods of the instant invention.

Additionally, the examiner stated that "[t]he specification does not disclose other modified peptide[s] that are effective against tumor growth or disclose the effectiveness of peptide[s] against different tumors" (office action at 5). The examiner indicates that the Y60L working example does not reasonably predict the activity of the genus, nor does the working example enable activity toward all tumors (citing *In re Dresfield*). Applicant, however, respectfully asserts that they are not required to demonstrate that each species of null IGF is effective in inhibiting the growth rate of a tumor and that the burden is on the examiner to assert why other species of null IGF would not work in slowing the tumor growth rate. *See*, *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Additionally, the examiner agrees that sufficient guidance is provided on how to make the claimed peptides of the present invention, i.e., null IGFs, but that "one of ordinary skill would be burdened with undue 'painstaking experimentation study' to determine if the peptides would be effective in slowing the growth rate of tumors in a subject having cancer" (office action at 7). Applicant respectfully disagrees. The specification provides a theoretical basis for the importance of the two properties, i.e., null IGF displaces native IGF-I from complexes with binding proteins...resulting in reduced IGF-I activity, which reduces growth of tumors" (Specification at 6, lines 22-25). The import of these two features narrows the genus substantially.

Moreover, the burden is on the examiner to provide an objective basis for determining that null IGFs, other than Y60L, will not work in the present invention. "Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation" (M.P.E.P. § 2164.02).

Continuing, the examiner asserted that "the specification does not set forth assay models whereby one could reasonably determine if the modification [of the peptide] achieved the desired 'little or no binding' to the type I IGF-I receptor" (office action at 6). Applicant respectfully disagrees. The binding affinity of Y60L toward the IGF-I receptor was known in the art to be approximately 20-fold lower than native IGF and therefore presents a suitable model for determining the parameters of "little or no binding." For example, since the data in the present invention indicates that the level of activity from Y60L is sufficient to elicit an anti-tumor effect, a null IGF which has similar binding characteristics to Y60L is also suitable for use in the present invention. Furthermore, the *in vivo* mouse model described in Applicant's working examples can also be used to determine if the modified IGF has the requisite binding characteristics and is able to slow tumor growth.

Moreover, based on the teachings of the present invention, one of ordinary skill in the art would readily appreciate that if a 20 fold reduction in affinity for the IGF receptor would work (as in the case of Y60L) , then a lower affinity analog would work as well. The critical point of the invention is to replace native IGF activity with a less potent IGF and therefore the multiple point mutants described in Bayne *et al. J. Biol. Chem.*, 265:15648 (1990) that exhibited even greater than 20 fold reductions in binding affinity are also suitable for use herein.

Accordingly, one skilled in the art would know what is meant by "little or not binding" and that the phrase in the present invention is interpreted as about 20-fold less or lower. This understanding is consistent with the working example described in the present invention.

Furthermore, while the examiner admitted thatY60L IGF-I "was shown to be affective [sic] against prostate cancer" (office action at 5), the examiner asserted that not all cancers "have the same mechanism of development and growth" and "that an agent effective against one tumor would not be effective against all types of tumors" (office action at 7). However, since the theorized mechanism of the null IGF is to limit the amount of native IGF activity (page 6, lines 21-25), cancers whose mechanism of growth and/or progression is IGF-I related are suitable for treatment with the methods described in the present invention.). For your convenience, relevant literature demonstrating the role of IGF in the growth and/or progression of lung, breast and colon cancer, is attached. *See*, Appendix B.

35 U.S.C. § 112, 2nd paragraph

The examiner rejected claims 7-9 for alleged indefiniteness. Applicant respectfully asserts that the examiner's rejection is flawed. Claims 7-9 do not lack antecedent basis for the limitation concerning positions in the base claim. Nevertheless, claims 7-8 have been amended to more clearly recite the invention. Support for these amendments can be found throughout the instant specification.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

Date 8/21/02

By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

7. (Amended) The method of claim 1, wherein the residue at position 60 of the amino acid sequence of said null IGF-I is altered to a non-aromatic residue.

8. (Amended) The method of claim 7, wherein the residue at position 24 or 31 of said amino acid sequence of said null IGF-I is additionally altered to a non-aromatic residue.

Following are the Protein Data Bank (PDR) records and the corresponding Medline Abstracts.

Description: Three-Dimensional Structure Of Human Insulin-Like Growth Factor-I (Igf-I) Determined By 1h-Nmr And Distance Geometry, 6 Structures.
Deposition: A.Sato, S.Nishimura, T.Ohkubo, Y.Kyogoku, S.Koyama, M.Kobayashi, T.Yasuda & Y.Kobayashi, 18-Aug-98
Taxonomy: Homo sapiens
Reference: PubMed MMDB: 10220 PDB: 1BQT

Description: Insulin-Like-Growth-Factor-1.
Deposition: E.De Wolf, R.Gill, S.Geddes, J.Pitts, A.Wollmer & J.Grotzinger, 11-Feb-99
Taxonomy: Homo sapiens
Reference: PubMed MMDB: 9568 PDB: 1B9G

Description: Insulin-Like Growth Factor Ii (Igf-Ii, Igf-2) (Nmr, 20 Structures).
Deposition: A.M.Torres, B.E.Forbes, S.E.Aplin, J.C.Wallace, G.L.Francis & R.S.Norton, 29-Dec-94
Taxonomy: Homo sapiens
Reference: PubMed MMDB: 1323 PDB: 1IGL